

**REMARKS**

The Office Action of April 1, 2009 has been carefully studied. Favorable reconsideration and allowance of the claims are respectfully requested.

**I. Claim Status and Amendments**

Claims 1-43 were pending in this application when last examined. Claims 1-7 and 10-43 stand rejected. No claims have been allowed.

Claims 8 and 9 are objected to for depending on a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. See page 21 of the Office Action. Applicants appreciate the Examiner's indication of allowable subject matter.

By way of the present amendment, Applicants have made amended claim 1 to clarify the micronail structure. Support can be found throughout the disclosure, for example, at page 5, lines 5-14, and page 12, lines 13-16 and Figure 5-7, in particular, Figure 6, and original claims 1-3. In addition, Applicants have made minor editorial revisions to the claims to address the formal matters raised in the Office Action, to correct punctuation, and to better conform to US practice with respect to antecedent basis. Such revisions are unrelated to patentability. The revisions are non-substantive and they are not intended to narrow the scope of protection. Applicants have also revised claim 31 to depend on claim 30 to provide antecedent basis for "coated gate."

New claims 44 and 45 have been added. New claim 45 depends on claim 21 and corresponds to the "such as" language removed from claim 21. Support for claim 44 can be found in the disclosure, for example, at page 3, lines 18-22.

Claims 2 and 5 have been cancelled without prejudice or disclaimer thereto. Applicants reserve the right to file a continuation or divisional application on any cancelled subject matter.

No new matter has been added by the above claim amendments.

Claims 1, 3, 4, and 6-45 are pending upon entry of this amendment, and these claims define patentable subject matter warranting their allowance for the reasons discussed herein. Applicants request favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

**II. Indefiniteness Rejection Under 35 U.S.C. § 112**

Claims 1-43 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the reasons in pages 2-4 of the Office Action. This rejection is respectfully traversed.

The claims have been amended to better define the claimed subject matter more clearly and distinctively in a non-narrowing manner to overcome this rejection.

First, in the middle of page 2, the examiner contends that though claim 1 recites "A surface-substrate" and "the surface" at lines 1 and 4, respectively, it is unclear whether "surface-substrate" means a combination of a surface and a substrate or a substrate having a surface. To address this concern, Applicants have amended independent claim 1 to "a substrate having a surface" as supported by description throughout. Dependent claims 2-24 have been amended accordingly.

Second, the examiner indicates that while claim 8 recites "wherein the hydrolytic enzyme is selected from polysaccharide-degrading enzymes, proteinases and lipid-degrading-enzymes", the claim depends from claim 5, which recites such hydrolytic enzymes as an

alternative. To address this concern, Applicants have amended claim 8 in the manner suggested by the examiner.

Third, the examiner notes that claim 32, in line 2, lacks antecedent basis for "the receptor molecules". To address this concern, Applicants have amended claim to recite "the recognition molecules" as suggested by the examiner.

Fourth, the examiner notes that while claim 29 (and claims 30-40 in view of their dependency thereon) recites "An electrode according to Claim 24, coated with a layer of immobilized recognition molecules that, in the presence of cell-secreted components, catalyze a reaction that causes release of ions in a media surrounding said recognition molecule", the claim depends from claim 1 and recites that the electrode which comprises the substrate-surface of claim 1 is coated with a layer of immobilized recognition molecules. In reply, Applicants have amended claim 29 to clarify that "at least a region of said electrode is coated" to better conform to US practice for antecedent basis. It is noted that Applicants have also revised claim 31 to depend on claim 30 to provide antecedent basis for "coated gate."

The amended claims are clear, definite and have full antecedent basis. Thus, the rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

### **III. Obviousness Rejections**

Claims 1-7, 10, 12, 13, 17-22, 24-28, and 41-43 are rejected under 35 U.S.C. § 103(a) as obvious over Lu et al. (WP 03/104789A1) in view of Yitzhaik et al. (WO 00/51191) for the reasons on pages 4-11 of the Office Action.

Claim 11 is rejected under 35 U.S.C. § 103(a) as obvious over Lu et al. in view of Yitzhaik et al. and further in view of Witt et al. (US 5,795,860) for the reasons on pages 11-12.

Claims 14 and 15 are rejected under 35 U.S.C. § 103(a) as obvious over Lu et al. and Yitzhaik et al. and further in view of Meyers et al. (US 4,546,083) for the reasons on pages 12-13.

Claim 16 is rejected under 35 U.S.C. § 103(a) as obvious over Lu et al. in view of Yitzhaik et al. and Meyers et al. and further in view of Singh et al. (US 7,270,973) for the reasons on pages 13-15.

Claim 23 is rejected under 35 U.S.C. § 103(a) as obvious over Lu et al. in view of Yitzhaik et al. and further in view of O'Connor et al. (US 20020009810A1) and Keeth et al. (US 6,465,331) for the reasons on pages 13-15.

Claims 29-35 and 37-40 are rejected under 35 U.S.C. § 103(a) as obvious over Lu et al. in view of Yitzhaik et al. and further in view of Blackburn et al. (US 6,846,654) for the reasons on pages 17-20.

Claim 36 is rejected under 35 U.S.C. § 103(a) as obvious over Lu et al. in view of Yitzhaik et al. and further in view of Blackburn et al. and O'Connor et al. for the reasons on pages 20-21.

These rejections are respectfully traversed and will be discussed together below, since Lu et al. and Yitzhaik et al. are used as the primary reference and the first secondary reference in each rejection. As all the claims depend, either directly or indirectly, from claim 1, it is believed that the arguments in favor of patentability for claim 1 suffice for all the claims.

The above-noted rejections should fall, because the combined cited prior art references fail to teach, suggest or make obvious all of the limitations of claim 1 (which is the sole independent claim), as required to support a *prima facie* case of obviousness.

To start, the Examiner's attention is drawn to the following:

The instant application relates to a substrate having a surface with nano-to micro scale protrusions in the form of "micronails". In this regard, independent claim 1 specifies that the "at least one micronail structure protruding from the surface, said micronail structure comprising a base rod-like portion and a head cap-like portion of a larger surface." Claim 1 further specifies that at least a region of said micronail structure within the head cap-like portion has cellular internalization-promoting moieties so that at least the head cap-like portion of the micronail structure has cellular-internalization promoting properties. Beyond this structure defining base and head portions, claim 1 requires that "at least a region of said micronail structure within the head cap-like portion has cellular-internalization promoting moieties so that at least the head cap-like portion of the micronail structure has cellular-internalization promoting properties. The cellular-internalization promoting properties enable the head cap-like portion of the micronail structure to be internalized by elements of the extracellular word via phagocytosis or endocytosis. Accordingly, the protrusions on the surface, namely at least the cap-like head portions, are thus internalized into the cell and the cellular membrane is wrapped around each such cap-like portion, and by this, the cell is adhered with a strong physical tight contact onto the surface of the claimed substrate.

Claim 1 has been amended to clarify the above-mentioned unique structural features of the micronail. These amendments are fully supported by the description in the specification, see for example, page 12 lines 11-13, which indicates "[T]hese protrusions are also termed hereinafter 'micronails' or 'nails' by one option, and they comprise a rod- or stem-like 'base' portion and may also comprise a 'head' portion." See also, the illustrated embodiment in Figure 6 and its corresponding description at page 20, lines 13-16, wherein it is disclosed that "[o]n top of the tungsten base, there is a cap (head portion) of gold or another metal such as for example copper, aluminum, platinum and silver, obtained by standard electroplating or

electrolyses plating technique, which is performed on the finished wafers." See the description at page 5, lines 10-13, wherein it is disclosed that "[t]ypically, the cellular-internalization promoting properties are a property of the head portion, although during the process of internalization many times both the head and the base portion are internalized by the cell."

Applicants respectfully submit that the prior art rejections should fall, because the cited prior art references fail to teach, suggest or make obvious all of the above-noted features of claim 1 (which is the sole independent claim), as required to support a *prima facie* case of obviousness.

As to the references of Lu et al. and Yitzhaik et al., these references, either alone or when combined, fail to disclose or suggest a substrate having at least one micronail structure protruding from the surface, in which the micronail structure comprises a base rod-like portion and a head cap-like portion of a larger surface, as required in claim 1.

Lu et al. relates to a biosensor having a substrate, a conductive thin film, a ZnO nanotip array on the conductive film and metal electrode pad. The nanotip array of Lu et al. differs completely in structure from the substrate and the micronail structure of claim 1 of the instant application. In particular, the configuration of the nanotip of Lu et al. does not include the features of a base portion or a head portion in the form of a rod-like portion and a cap-like portion, respectively, which are essential features in the structure of the micronail of claim 1 that enable the capability of engulfment. Thus, it is clear that Lu et al. lacks the structural elements of the micronail structure, as well, as the recited cellular internalization-promoting moieties of claim 1, necessary for the cellular internalization promoting properties.

Further, it should be noted that the purpose of the structure of the device in Lu et al. is for sensing molecules in a sample, and the protrusions used there are intended to increase the contact area, and consequently the effective sensing area, and therefore, to improve the

sensing and detection efficiency. The technique of Lu et al. is also intended to bind target molecules. Lu et al. is completely silent as regards to cells in general, and immobilizing cells on the surface, and thus, it does not provide a suggestion for using surface recording and stimulation of live whole cells.

By contrast, the claimed substrate of the instant application makes use of the natural phenomena of phagocytosis, whereby cells engulf solid particles by the cell membrane to form an internal phagosome. The solid particles are typically in nature as bacteria and other cells having rounded structures. To encourage the natural “engulfing” properties of the cells, the shape to be swallowed has to be similar to the shape naturally phagocytosed, *i.e.*, the cap shape of the micronail according to claim 1. However, the pyramidal-like shapes, with needle-like tips, such as those in Lu et al., are incapable of inducing phagocytosis. In this sense, it is believed that the pyramidal-like shapes with needle-like tips in Lu et al. have a completely different structure and function from the claimed substrate and protruding micronail structure comprising a base rod-like portion and a head cap-like portion of a larger surface, with the cellular internalization-promoting moieties.

Furthermore, to produce a tight seal of the membrane around the base of the structure allowing effective electrical reading and stimulation between the micronail and the cell, the region around which the membrane closes has to be narrower than the region which is internalized by the cell. The cap-rod shape of the claims of the instant application is therefore an optimal shape for internalization.

Contrary to the structure of claimed substrate and micronail, the shape of the needle-like tips in the technique of Lu et al. becomes progressively wider from the tip towards the base and therefore would not allow effective closing of the membrane around the “engulfed”

region. Indeed, the examiner at page 6 of the Office Action acknowledges that "Lu et al. do not teach that the micronail structure has cellular-internalization promoting properties."

It is believed that this disclosure of the pyramidal-like shapes with needle-like tips in Lu et al. actually teaches away from the base rod-like portion and a head cap-like portion of a larger surface with the cellular internalization-promoting moieties of claim 1. It is well established that a prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). M.P.E.P., Eighth Ed., Rev. 6 (September 2007) at § 2141.02, VI. A prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness. M.P.E.P., Eighth Ed., Rev. 6 (September 2007) at § 2145, X, D, 1. If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959); M.P.E.P., Eighth Ed., Rev. 6 (September 2007) at § 2143.01, VI.

Accordingly, the skilled artisan, upon reading Lu et al., would be motivated to use the pyramidal-like shapes with needle-like tips of Lu et al., and not the base rod-like portion and the head cap-like portion of a larger surface with the cellular internalization-promoting moieties of claim 1. Thus, the combination of t Lu et al. and Yitzhaik et al. would not have led one skilled in the art, at the time the invention was made, to produce the claimed substrate having at least one micronail structure protruding from the surface, wherein the micronail structure comprises a base rod-like portion and a head cap-like portion of a larger surface of claim 1.

Therefore, to summarize, Lu et al. (1) does not mention whole cells and reading and stimulating from whole cells; (2) the pyramidal shape structures of Lu et al. publication are

not of a suitable shape to be naturally internalized by cells, and such shape in Lu et al. actually teaches away from the claimed features, and (3) the tips have progressively expanding structures which are not suitable for the closing of the membrane of the cells around them and to provide a tight seal.

Based on the above, it should be clear that the structure in Lu et al. is completely different from, and indeed is not suggestive of, and actually teaches away from the structure of the claimed substrate having at least one micronail structure protruding from the surface, wherein the micronail structure comprises a base rod-like portion and a head cap-like portion of a larger surface of claim 1.

For these reasons, the primary reference of Lu et al. fails to disclose or suggest each and every element of independent claim 1. Accordingly, claim 1 is believed to be novel and patentable over Lu et al.

The secondary reference of Yitzchaik et al. does not cure the above-noted deficiency of Lu et al. Yitzchaik et al. teaches about moieties that enable tight binding of the cell to a substrate.

The patent application of Yitzchaik et al. discloses an electrical junction enabling the coupling between electrical devices and voltage sensitive cells (VSC). The VSC are anchored to the external surface of the transistor by a plurality of binding moieties such as antibodies, receptors, ligands, lectins and adhesion molecules. However, the cellular-internalization-promoting biological properties of such moieties as in Yitzchaik et al. are not mentioned at all and cannot be gleaned from the patent application. Nowhere does Yitzchaik et al. mention such properties. Further, Yitzchaik et al. does not mention any sort of protrusions in general and of the shape that can be internalized in particular. Thus, not only does Yitzchaik et

al. fail to suggest using such moieties in the manner required in the claims, but the reference also fails to disclose the structure of the claimed micronails.

Moreover, even if the pyramid-like protrusions of the technique of Lu et al. were covered by the cell binding moieties of Yitzchaik et al, such an arrangement would not be sufficient to induce internalization using a phagocytosis mechanism (due to the non-natural sharp shape of the tip described in Lu et al.), and as a consequence it would not form a tight seal of the cellular membrane around the base of the protrusion (due to the fact that the base is wider than the tip). Thus, it should be clear that the combination of Lu et al. and Yitzchaik et al. fails to meet each and every element of claim 1.

It should also be noted that the examiner's interpretation that "mere binding of the cells appear to be convey cellular-internalization property on the nanotip" is actually incorrect. For effective internalization and formation of a tight seal around the engulfed object, the shape of the protrusion should be of the cap-rod as defined in the amended claim 1. Again, for the reasons discussed above, the combination of Lu et al. and Yitzchaik et al. would not result in this structure.

Therefore, the combination of Lu et al. and Yitzchaik et al. would not result in each and every feature of claim 1, especially cap-rod like micronails having cellular-internalization promoting properties and having a shape that encourages the natural phagocytic properties of the cell and that allow formation of a tight seal around the base of the structure (eliminating leakage of cellular components as well as of electrical current). In fact, the combination of Lu et al. and Yitzchaik et al. actually teaches away from such claimed features. Thus, claim 1 and all claims dependent thereon are believed to be novel and patentable over Lu et al. and Yitzchaik et al.

Therefore, the obviousness rejection of claims 1-7, 10, 12, 13, 17-22, 24-28, and 41-43 over Lu et al. and Yitzchaik et al. is untenable and should be withdrawn.

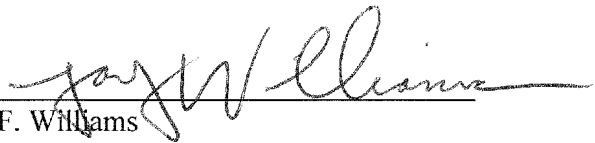
As to the remaining obviousness rejections, it should be noted that these rejections utilize a combination of Lu et al. and of Yitzchaik et al. with one or more of Witt et al., Meyers et al., O'Connor et al., Keeth et al., and Blackburn et al. However, Witt et al., Meyers et al., O'Connor et al., Keeth et al., and Blackburn et al. fail to remedy the above-noted deficiencies of Lu et al. and Yitzchaik et al. Indeed, these other secondary references were only relied upon as allegedly disclosing the features of other dependent claims. They do not disclose or suggest the elements of claim 1. Thus, the obviousness rejections utilizing a combination of Lu et al. and of Yitzchaik et al. with one or more of Witt et al., Meyers et al., O'Connor et al., Keeth et al., and Blackburn et al. are also untenable and should be withdrawn. Withdrawal of these rejections is therefore solicited.

**VI. Conclusion**

All issues raised in the Office Action have been fully addressed in a manner that should lead to patentability of the present application. Favorable consideration and allowance are respectfully requested. If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.  
Attorneys for Applicant(s)

By   
Jay F. Williams  
Registration No. 48,036

JFW:pp  
Telephone No.: (202) 628-5197  
Facsimile No.: (202) 737-3528  
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